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IL28B rs12979860 and rs8099917 polymorphisms in patients with chronic hepatitis C and non-viral liver disease

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Abstract

Aim: In this study, we aimed to evaluate the relationship of IL28B rs12979860 and rs8099917 polymorphisms with the clinical, histological and virological outcomes of patients with chronic hepatitis C and non-viral liver disease, and also the treatment responses of patients with chronic hepatitis C, who received direct-acting antiviral (DAA) therapy.

Material and Methods: A total of 142 patients, 59 of whom had chronic hepatitis C, and 83 of whom had liver biopsy for different clinical indications, were included in the study. The IL28B rs12979860 and rs8099917 polymorphism were genotyped using the TaqMan assay.

Results: IL28B rs12979860 CC and IL28B rs8099917 TT were identified as the genotypes with the highest frequency in all patients, and patient groups included in the study. On the other hand, IL28B rs12979860 TT and IL28B rs8099917 GG were the genotypes with the lowest frequency. No significant association was found between IL28B rs12979860 and IL28B rs8099917 polymorphisms and clinical and histopathological outcomes of patients as well as DAA treatment responses in patients with hepatitis C.

Discussion: IL28B rs12979860 and rs8099917 polymorphisms do not affect clinical and histopathological outcomes of patients with chronic hepatitis C and non-viral liver diseases as well as with DAA treatment.

Keywords

Interleukin 28B, Chronic Hepatitis C, Non-Viral Liver Disease, Treatment Response

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Introduction

Hepatitis C Virus (HCV) is a substantial public health concern owing to its progressive clinical outcomes with higher morbidity and mortality, such as chronic active hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). HCV infection affects more than 150 million people worldwide. The natural course of chronic HCV infections and host factors of the virus-infected individuals can be determinative of the pathogenesis and progression of the liver diseases with which they are associated. The human immune system can impact the pathogenesis, clinical course, and outcomes of viral and non-viral liver diseases [1,2]. Interferons lambda (IFN-λs; IFNL1-4), classified as type III IFN, is a cytokine that plays a role in the formation of antiviral immune responses, encoded by IFNL3 interleukin 28B (IL28B), which mostly acts on epithelial surfaces [3].

It has been suggested that IL28B rs12979860 and rs8099917 polymorphisms may be associated with spontaneous clearance and clinical and histological outcomes of chronic viral hepatitis caused by HCV. In general, IL28B rs12979860CC and rs8099917 TT genotypes are reported as favorable genotypes due to the reduced risk of advanced liver damage such as HCV-related cirrhosis and HCC, and the positive effects on the clinical course and outcomes of the patients as well. On the other hand, the genotypes characterized by the presence of CT and TT polymorphisms for rs12979860 and TG and GG minor allele polymorphisms for rs8099917 are considered unfavorable genotypes due to their negative effects on the clinical course and outcomes of patients with HCV-related increased risk of cirrhosis, and HCC [4-8]. Some studies have reported that there is no relationship between IL28B rs1297986 and rs8099917 polymorphisms and the virological and clinical outcomes of patients. In addition, they found no correlation between IL28B rs1297986 and rs8099917 polymorphisms and the risk of developing HCV-related cirrhosis and HCC [9-12].

It has been reported that IL28B rs12979860 CC and IL28B rs8099917 TT genotypes are strongly associated with treatment and sustained virologic responses (SVR) in patients with chronic hepatitis C after IFN-based antiviral treatments. However, the data on the effects of IL28B rs12979860 and rs8099917 genotypes on treatment response of patients with chronic hepatitis C receiving direct-acting antiviral therapy (DAA) therapy are limited [5,13].

In addition, it has been suggested that IL28B rs12979860 and rs8099917 gene polymorphisms may have an impact on the formation of non-viral liver diseases, especially non-alcoholic fatty liver disease (NAFLD). However, the data on such a suggestion is quite limited [14-16]. In general, there is no consensus on the relationship between IL28B polymorphisms and liver pathologies that may develop due to viral or non-viral factors. In addition, most studies conducted for this purpose included patients who developed HCV-related cirrhosis and HCC. The data on the association of IL28B polymorphisms with liver histology and clinical and virological characteristics of patients with chronic hepatitis C are limited.

In this study, we aimed to evaluate the IL28B rs12979860 and rs8099917 gene polymorphisms among the patients with chronic hepatitis C and non-viral chronic liver disease and also treatment responses of patients with chronic hepatitis C who received DAAs therapies.

Material and Methods

Ethical approval for the study was provided by Istanbul Medical School Ethics Committee at Istanbul University (No: 2018/895).

Patients: The present study included a total of 142 patients were followed up by the Gastroenterohepatology Department of Istanbul University Istanbul Medical School, 59 for chronic hepatitis C, and 83 whose liver parenchymal biopsy was performed due to different clinical indications other than viral hepatitis agents. Biopsy indications of patients who underwent liver parenchyma biopsy except for viral hepatitis agents consisted of metabolic liver disease 32 (38.5%), cholestatic liver disease 16 (19.3%), elevated liver enzymes unknown of cause 18 (21.7%), elevated autoimmune antibodies 5 (6.0%), cirrhosis 4 (4.8%), vascular liver disorders 4 (4.8%), toxic hepatitis 3 (3.6%), and granulomatous liver diseases 1 (1.2%).

A total of 142 patients, 59 of whom were diagnosed with chronic hepatitis C and 83 with non-viral liver disease, had seronegative hepatitis B virus surface antigen (HBsAg). Anti-HCV antibodies of patients with defined non-viral liver disease were seronegative. All patients were seronegative for human immunodeficiency virus (HIV) antibodies.

Clinical materials: Liver biopsies were performed in the Interventional Radiology Unit of the Radiology Department and in the Gastroenterohepatology Department of Internal Medicine, at Istanbul Medical School. One set of liver-tissue specimens was preserved in Hollande's fixative and sent to the Pathology Department for evaluation. A second tissue fragment or another biopsy sample was immediately snap-frozen in liquid nitrogen and kept at 80°C before use for genotype analysis.

DNA extraction from liver-biopsy specimens: Total genomic DNA was extracted from each liver-tissue sample using a commercially available kit (QIAamp DNA Mini kit, Qiagen GmbH, Hilden, Germany). Total DNA was purified according to the manufacturer's recommendations. DNA concentrations were determined using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA).

IL28B genotyping: IL28B rs12979860 rs8099917 was typed using the standard TaqMan SNP Genotyping Assay. The allele discrimination plot and results were then generated using StepOne Software (Applied Biosystems, Foster City, CA, USA).

Liver histopathology: Histology of liver biopsy specimens was evaluated in the Department of Pathology of Istanbul Medical School, Istanbul University. Liver biopsy samples were fixated in a formalin solution and stained with Masson's trichrome. Pathology reports contained histological parameters including fibrosis, portal and lobular inflammation, lobular necrosis, steatosis, cholestasis, and bile duct damage. Inflammation and fibrosis for chronic hepatitis C patients were assessed using the modified Ishak scoring system [17]. Patients were divided into groups in terms of inflammation: minimal/mild (0–7), moderate (8–11), and severe (12–18), and fibrosis: none (0) mild (1), moderate/severe (2–4), and cirrhosis (5–6). NAFLD was defined as the observation of abnormal lipid accumulation (hepatic steatosis) in more than 5% of hepatocytes. NASH was defined as the presence of lobular inflammation together with ballooning (hepatocyte damage) and hepatic steatosis, with

or without fibrosis [18]. In histopathological diagnosis, the presence of minimal portal or lobular inflammatory infiltrates, absence of fibrosis, and absence of structural changes was considered non-specific histological findings.

Clinical laboratory data: Demographics and pre-biopsy patient data, including HCV RNA viral load, and HCV genotypes were obtained from patient files or from the hospital's electronic data management system (Table 1). Viral load of patients with chronic hepatitis C was classified as low (400000 IU/ml) or high (400000 IU/ml), in accordance with Witthöfft et al. [19].

DAA treatment and sustained virologic responses:

Dasabuvir/Ritonavir+Ombitasvir+Paritaprevir treatment was given to 74.50% (38/51) of the patients. Of the remaining patients, 3 received Sofosbuvir+Ledipasvir, 3 received Dasabuvir/Ritonavir+Ombitasvir+Paritaprevir/Ribavirin, 1 Ribavirin/Sofosbuvir+ Ledipasvir, 1 sofosbuvir/ribavirin, and 1 Glecaprevir+Pibrentasvir. Dasabuvir/Ritonavir+Ombitasvir+Pari taprevir treatment was given to 2 of the 4 patients who were found to have treatment failure after interferon (IFN)-based treatment, and Sofosbuvir+Ledipasvir/Ribavirin treatment was applied to the other 2 patients. SVR is defined as undetectable HCV-RNA in serum or plasma 24 weeks after the end of therapy [20]. In order to evaluate the effect of IL28B rs12979860 and rs8099917 polymorphisms on SVR after DAA treatment, 51 patients whose serum HCV RNA results could be obtained at least 24 weeks after treatment were included. Finally, the absence of SVR or a relapse after treatment was defined as treatment failure.

Statistical analysis

Descriptive statistics were used to describe continuous variables (mean, standard deviation). Comparison of two independent and normally distributed variables was performed using the Student's t-test. Comparison of two independent and non-normally distributed variables was made using the Kruskal-Wallis or Mann-Whitney U test. The independent variable effects on the dichotomous dependent variable were investigated by Logistic Regression Analysis. Analyzes were performed using IBM SPSS Version 25.0 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Linkage disequilibrium (LD) between pairwise SNPs, was calculated using Haploview software. Hardy-Weinberg equilibrium (HWE), allele frequencies, and genotype distributions were analyzed using the chi-square test. The statistical significance level was determined as 0.05.

Results

Demographic, clinical, and histopathological characteristics of patients

Table 1 summarizes the demographic, clinical, clinical laboratory, and histopathological data of the total 142 patients, 59 of them with chronic hepatitis C, and 83 of them with non-viral liver disease. Histologically, the mean inflammation grade in patients with chronic hepatitis C was 6.00 ± 2.1, and the mean fibrosis stages 2.59 ± 1.13. histopathological diagnoses of 83 patients who underwent liver biopsy for different non-viral clinical indications are summarized in Table 1. Accordingly, the most histopathologically reported finding was liver steatosis, with a total of 33 (39.8%) patients with 22 (26.5%) NASH, and 11 (13.2%) NAFLD.

Genotype and frequency of IL28B rs12979860 and rs8099917

The genotypes and frequencies detected for IL28B rs12979860 and rs8099917 polymorphisms in this study are shown in Tables 2 and 3. IL28B rs12979860 CC (42.37%) and IL28B rs8099917 TT (57.63%) were identified as the genotypes with the highest frequency for chronic hepatitis C patients. IL28B rs12979860 CC (43.37%) and CT (43.37%) and also IL28B rs8099917 TT (63.86%) were identified as the genotypes with the highest frequency for chronic hepatitis C patients. On the other hand, IL28B rs12979860 TT and IL28B rs8099917 GG were the genotypes with the lowest frequency for all patients. No deviation from HWE for rs12979860 and rs8099917 at IL28B gene was found in both patient groups (x2 tests, $p \geq 0.05$).

IL28B polymorphisms in patients with chronic hepatitis C

HCV genotype was 1B in 52 (88.13%) patients with chronic hepatitis C included in this study, 1A in 6 (10.16%) and, 3B in 1 (1.69%) (Table 2). As shown in Table 2, no significant association was found between IL28B rs12979860 and IL28B rs8099917 polymorphisms; and demographic, clinical laboratory, virological including viral genotype and viral loads of chronic hepatitis C patients and as well as histological data including necro-inflammatory activity grade and fibrosis stages of patients.

Table 1. Demographic, clinical, clinical laboratory and histopathological characteristics of the patients

Data	Chronic hepatitis C n: 59	Non-viral liver disease n: 83
Mean age ± SD (years)	56.08 ± 16.39	47.48 ± 13.81
Gender (M/F)	19/40	38/45
Clinical laboratory		
ALT (U/L), Mean±SD	72,42 ± 173,07	96,69 ± 148,85
AST (U/L), Mean±SD	69,03 ± 99,97	114,23 ± 141,29
ALP (U/L), Mean±SD	80,31 ± 27,46	171,4 ± 207,59
GGT (U/L), Mean±SD	56,85 ± 58,14	174,51 ± 246,14
Total bilirubin (mg/dl), Mean±SD	0,56 ± 0,33	1,04 ± 1,43
Direct bilirubin (mg/dl), Mean±SD	0,4 ± 1	0,63 ± 1,26
Indirect bilirubin (mg/dl), Mean±SD	0,31 ± 0,22	0,37 ± 0,24
INR, Mean±SD	1,01 ± 0,08	1 ± 0,12
AFP (ng/ml), Mean±SD	3,68 ± 2,28	3,65 ± 3,38
Albumin (g/dl), Mean±SD	4,43 ± 0,7	4,31 ± 0,6
Platelet count (106/ml), Mean±SD	210,51± 36,75	223,53 ± 77,03
Histology		
Inflammation (Grade) Mean±SD	6.00 ± 2.1	
Fibrosis (Stage), Mean±SD	2.59 ± 1.13	
Liver steatosis/Hepatic steatosis	NA	33 (39,8)
NASH	NA	22 (26,5)
NAFLD	NA	11 (13,2)
Non-specific changes*	NA	23 (27,7)
Cholestatic Liver disease**	NA	14 (16,9)
Cirrhosis	NA	4 (4,8)
Portal hypertension/Venopathy	NA	4 (4,8)
Toxic hepatitis	NA	3 (3,6)
Granulamatous liver diseases	NA	1 (1,2)
Autoimmune hepatitis	NA	1 (1,2)

Abbreviations: ALT; alanine aminotransferase, AST; aspartate aminotransferase, ALP; alkaline phosphatase, GGT; gamma-glutamyl transferase, INR; international normalized ratio, AFP; serum alpha-fetoprotein, NASH; Non-alcoholic steatohepatitis, NAFLD; Non-alcoholic fatty liver disease, NA; not applicable. *Non-specific changes; minimal portal or lobular inflammatory infiltrates, absence of fibrosis, no structural changes in histopathological diagnosis, **Cholestatic Liver disease; Biliary disease (PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis)

Table 2. Demographic, clinical laboratory, virological histological characteristics and response treatment with IL28B polymorphisms of patients with chronic hepatitis C

Data	rs12979860				rs8099917			
IL 28B genotype	CC n (%)	CT n (%)	TT n (%)	p	TT n (%)	TG n (%)	GG n (%)	p
Frequency	25 (42,37)	24 (40,68)	10 (16,95)	n.s.	34 (57,63)	23 (38,98)	2 (3,39)	n.s.
Mean age ± SD (years)	57,88±15,39	55,04±18,64	54,1±13,95	n.s.	54,1±13,95	56,35±16,89	52±16,97	n.s.
Gender (M/F)	9/16	9/15	1/9	n.s.	1/9	7/16	0/2	n.s.
Clinical laboratory								
ALT (U/L), Mean±SD	105,32±260	52,38±53,11	38,25±13,73	n.s.	93,47±225,76	44,72±29,74	33±4,24	n.s.
AST (U/L), Mean±SD	81,84±120,19	66,96±97,48	41,99±18,13	n.s.	83,68±127,47	49,13±34,15	49±25,46	n.s.
ALP (U/L), Mean±SD	82,32±23,88	80,08±34	75,8±18,77	n.s.	80,74±24,5	80,91±32,02	66±31,11	n.s.
GGT (U/L), Mean±SD	67,36±73,26	50,38±46,56	46,1±37,25	n.s.	61,71±67,2	48,26±41,04	73±83,44	n.s.
AFP (ng/ml), Mean±SD	3,92±3,13	3,58±1,17	3,34±1,87	n.s.	3,79±2,77	3,37±1,18	5,45±2,9	n.s.
VIRAL FACTORS								
HCV RNA log10 IU/ml (ort,SD)	5,27E+07 + 1,67E+08	4,03E+06 + 5,84E+06	3,58E+06 + 5,87E+06	n.s.	4,02E+07 + 1,44E+08	3,60E+06 + 4,77E+06	5,71E+05 + 1,41E+05	n.s.
<400. 000 IU/ml	3 (5,08)	7 (11,86)	0 (0,00)	n.s.	3 (5,08)	7 (11,86)	0 (0,00)	n.s.
>400.000 IU/ml	22 (37,29)	17 (28,81)	10 (16,95)	n.s.	31 (52,54)	16 (27,12)	2 (3,39)	n.s.
HCV Genotypes: 1B/1A/3A	19.01.2001	23.05.2000	10/0/1	n.s.	31/2/0	19.04.2001	2/0/0	n.s.
Histology								
Inflammation (Grade) Mean±SD	6,32±2,34	6.08+2.00	5.00+1.49	n.s.	6.35+2.17	5.57+2.00	5.00+1.41	n.s.
Fibrosis (Stage), Mean±SD	2,8±1,119	2,58±1,1	2,1±0,99	n.s.	2,68±1,12	2,43±1,2	3±0	n.s.
Treatment with DAA								
Dasabuvir / Ritonavir+Ombitasvir+Paritaprevir	12	18	8	n.s	20	17	1	n.s
Other DAA regimens*	7	4	2	n.s	8	5	1	n.s
SVR/failure treatment	18.Oca	22/0	10/0	n.s	27.Oca	22/0	2/0	n.s.

DAAs; Direct Acting antivirals, SVR: sustained virological response, n.s: not significant. * Indicated in the text, Major allele: C. Minor allele: T. for rs12979860. Major allele: T. Minor allele: G. for rs8099917. HWE: Hardy-Weinberg Equilibrium was P-value >0.05 for all patients. Abbreviations: NASH; Non-alcoholic steatohepatitis, NAFLD; Non-alcoholic fatty liver disease, n.s: not significant. *Non-specific changes; a minimal portal or lobular inflammatory infiltrates, absence of fibrosis, no structural changes in histopathological diagnosis; **Cholestatic Liver disease; Biliary disease (PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis)

Table 3. Histopathological characteristics of patients with non-viral liver disease and IL-28 gene polymorphisms

Data	rs12979860				rs8099917			
IL 28B genotype	CC n (%)	CT n (%)	TT n (%)	p	TT n (%)	TG n (%)	GG n (%)	p
Frequency	36 (43,37)	36 (43,37)	11 (13,25)	n.s.	53 (63,86)	27 (32,53)	3 (3,61)	n.s.
Histology								
Liver steatosis (n=33)								
NASH (n: 22)	10 (45,45)	8 (36,36)	4 (18,18)	n.s.	16 (72,72)	5 (22,72)	1 (4,54)	n.s.
NAFLD (n: 11)	6 (54,55)	4 (36,36)	1 (9,09)	n.s.	6 (54,55)	4 (36,36)	1 (9,09)	n.s.
Non-specific changes* (n=23)	6 (26,09)	15 (65,22)	2 (8,70)	n.s.	10 (43,48)	13 (56,52)	0 (0,00)	n.s.
Others								
Cholestatic Liver disease** (n=14)	8 (57,14)	6 (42,86)	0 (0,00)	n.s.	13 (92,86)	1 (7,14)	0 (0,00)	n.s.
Cirrhosis (n=4)	2 (50,00)	1 (25,00)	1 (25,00)	n.s.	2 (50,00)	1 (25,00)	1 (25,00)	n.s.
Portal hypertension/Venopathy (n=4)	2 (50,00)	1 (25,00)	1 (25,00)	n.s.	3 (75,00)	1 (25,00)	0 (0,00)	n.s.
Toxic hepatitis (n=3)	1 (33,33)	1 (33,33)	1 (33,33)	n.s.	1 (33,33)	2 (66,67)	0 (0,00)	n.s.
Granulamatous liver diseases (1)	0 (0,00)	0 (0,00)	1 (100,00)	n.s.	1 (100,00)	0 (0,00)	0 (0,00)	n.s.
Autoimmune hepatitis (1)	1 (100,00)	0 (0,00)	0 (0,00)	n.s.	1 (100,00)	0 (0,00)	0 (0,00)	n.s.

Association of IL-28B polymorphism and outcomes of DAAs treatment in patients with chronic hepatitis C

In this study, HCV RNA was not detected in serum/plasma samples taken at least 24 weeks after the completion of their treatment in all but one of the patients with chronic hepatitis C who received DAA treatment (Table 2). Treatment failure, characterized by the presence of viral relapse was described in a patient with HCV genotype 1B who had histologically defined cirrhosis. The same patient received Ribavirin/Sofosbuvir + Ledipasvir therapy and subsequently developed hepatocellular carcinoma (HCC).

IL-28B polymorphisms in patients with non-viral liver diseases

Table 3 summarizes the histopathological data of non-viral liver disease patients, as well as their IL28B genotypes and frequencies. Briefly, there was no significant association in 33 (39.8%) patients with histopathological liver steatosis, in 23 (27.7%) patients with non-specific changes, and in 27 (32.5%) patients with liver disease other than the above-mentioned causes in terms of L28B rs12979860 and IL28B rs8099917 polymorphisms.

Discussion

In this study population, the frequencies of IL28B rs12979860 CC and CT and also IL28B rs8099917 TT, described as favorable genotypes, were determined as 61 (%42.96) and 87 (%61.27), respectively. There was also no difference in the frequency distributions of these genotypes between the observed groups (Table 2 and 3). The relationship between polymorphisms near the IL28B gene and occurrence, progression, and outcomes of viral or non-viral liver diseases is quite challenging because of the studied geography, the genetic background of populations, characteristics and extent of patient groups, and other various factors, such as viral factors and so on.

In this study, no relationship was identified between rs12979860 and rs8099917 and histopathological results of patients with hepatitis C, including demographics, virological genotypes, viral loads, and clinical characteristics, including clinical laboratory findings, and HCV-related liver damage stages. It has been reported in some studies conducted for similar purposes that polymorphisms characterized by the presence of T alleles for IL28B rs12979860 and G alleles for rs8099917 were associated with the risk of developing advanced liver damage such as HCV genotype I-related cirrhosis and HCC [6,21,22].

However, the effects of IL28B rs12979860 and rs8099917 polymorphisms on the histological results of patients with chronic hepatitis C may be associated with viral genotypes. In this respect, favorable genotypes, especially IL28B rs12979860CC and rs8099917 TT genotypes, have also been reported that may cause advanced clinical outcomes with HCV other than genotype I, and hepatic damage and adverse effects [23] However, different studies have reported that IL28B rs12979860 and rs8099917 polymorphisms are not associated with HCV-related liver damage and disease progression, regardless of viral genotype [9,12].

It has been revealed in a small number of studies carried out to determine the relationship between IL28B rs12979860 and rs8099917 polymorphisms and viral genotype, viral load, and clinical laboratory data of patients with chronic hepatitis C, that especially IL28B rs12979860 CC genotype may be associated with higher ALT and higher serum HCV RNA levels [9,21]. On the other hand, it was found that IL28B rs12979860 and rs8099917 polymorphisms in patients with chronic hepatitis C were not associated with the demographic HCV genotype of the patients, and liver fibrosis stages. In the same study, they revealed that individuals carrying IL28B rs12979860 TT or CT genotypes have a higher likelihood of developing chronic hepatitis after HCV infection [24].

It has been reported that the presence of the CC genotype and C allele for IL28B rs12979860, and the presence of the TT genotype and T allele for rs8099917 are associated with SVR in IFN-based anti-viral treatments in patients with chronic hepatitis C, regardless of viral genotype. Additionally, it has been reported that the presence of minor alleles T and G, respectively, may be associated with unsuccessful treatment responses [5,6]. Nevertheless, the effect of IL28B polymorphisms on the outcome of patients with hepatitis C receiving DAA therapy is not clear yet. In a study conducted to evaluate such outcomes, IL28B rs12979860 TT genotype and T allele were found to be significantly associated with failure in achieving SVR [25]. The data obtained in this study indicate that IL28B rs12979860 and rs8099917 polymorphisms are not associated with SVR after the DAA treatment.

The results of the limited number of studies to determine the relationship between non-viral chronic liver diseases and IL28B polymorphisms are inconsistent and unclear (20-22). This study suggests that there is no direct relationship between IL28B rs12979860 and rs8099917 polymorphisms and non-viral liver diseases, based on the histopathological data of patients with non-viral liver disease and the IL28B rs12979860 and rs8099917 genotypes and frequency distributions detected in these patient groups.

The limited number of patients with chronic hepatitis C and non-viral liver disease included in this study and the lack of homogeneous distribution between the groups, as well as the low number of patients with advanced liver damage such as HCV-associated cirrhosis, were limiting factors for this study. Hereafter, this study included patients with histologically chronic hepatitis, then advanced liver damage such as HCV-associated cirrhosis and HCC.

Conclusion

It is suggested according to the data obtained from this study that IL28B rs12979860 and rs8099917 polymorphisms are not associated with the clinical and histopathological outcomes of viral hepatitis C and non-viral liver diseases as well nor with DAA treatment responses in patients with hepatitis C.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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